Seizure 41 (2016) 141–153

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Review

Non-EEG seizure detection systems and potential SUDEP prevention: State of the art
Review and update

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ARTICLE INFO

Article history:
Received 25 March 2016
Received in revised form 18 July 2016
Accepted 20 July 2016
Available online xxx

Keywords:
Epilepsy
SUDEP
Sudden unexpected death
Non-EEG based seizure detection
Alarm system

ABSTRACT

Purpose: Detection of, and alarming for epileptic seizures is increasingly demanded and researched. Our previous review article provided an overview of non-invasive, non-EEG (electro-encephalography) body signals that can be measured, along with corresponding methods, state of the art research, and commercially available systems. Three years later, many more studies and devices have emerged. Moreover, the boom of smart phones and tablets created a new market for seizure detection applications.
Method: We performed a thorough literature review and had contact with manufacturers of commercially available devices.
Results: This review article gives an updated overview of body signals and methods for seizure detection, international research and (commercially) available systems and applications. Reported results of non-EEG based detection devices vary between 2.2% and 100% sensitivity and between 0 and 3.23 false detections per hour compared to the gold standard video-EEG, for seizures ranging from generalized to convulsive or non-convulsive focal seizures with or without loss of consciousness. It is particularly interesting to include monitoring of autonomic dysfunction, as this may be an important pathophysiological mechanism of SUDEP (sudden unexpected death in epilepsy), and of movement, as many seizures have a motor component.
Conclusion: Comparison of research results is difficult as studies focus on different seizure types, timing (night versus day) and patients (adult versus pediatric patients). Nevertheless, we are convinced that the most effective seizure detection systems are multimodal, combining for example detection methods for movement and heart rate, and that devices should especially take into account the user's seizure types and personal preferences.

1. Introduction

Next to epilepsy treatment, epilepsy management including quality of life (QoL) and care becomes more and more important. A lot of research needs to be done before seizure prediction devices become available though, and as Mormann et al. [1] stated: "Prediction algorithms must be proven to perform better than a random predictor before prospective clinical trials involving seizure intervention techniques in patients can be justified." In the mean time, extracerebral seizure detection in patients

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http://dx.doi.org/10.1016/j.seizure.2016.07.012
1059-1311/

refractory to treatment is increasingly and internationally researched the last ten years (first published study in 2005 [2]) but still, no reliable product has appeared on the market, as proven by publications validating these products and our own experience.

A listing of non-EEG (electro-encephalography) body signals that can be measured, along with corresponding methods, state of the art research, and commercially available systems was submitted to '*Seizure*' in its final version on February 14, 2013 (review article accepted February 16, 2013 [3]), and since then, 11 studies (fulfilling the eligibility criteria mentioned further) and 8 commercially available devices have been added, showing the increasing interest in non-EEG based seizure detection. Moreover, the boom of smart phones and tablets has created a new market for development of seizure detection applications by researchers, small startup companies and even individuals or garage based operations whose founders have a loved one with epilepsy [4]. These can be coupled with widely available fitness or smart watches that usually detect movement and/or heart rate. This review article gives an updated overview.

2. SUDEP

A large amount of epilepsy-related deaths are accounted to SUDEP (sudden unexpected death in epilepsy). As the name says, the cause of death is unknown, but cardiac, respiratory and other autonomic dysfunctions have been thoroughly investigated and proposed as pathophysiological mechanisms. This makes it particularly interesting to include methods for monitoring cardiac, respiratory and other autonomic body signals in seizure detection systems.

SUDEP being a sensitive topic and mechanisms being unclear, most clinicians rarely, if ever, discuss it with their patients except when the patient is young, non-compliant, and the physician tries to 'scare them straight'. This brings up the discussion on whether a clinician should raise the subject, to whom, how and what should be discussed. Patient education on medication compliance, supine sleep position and lattice pillows, a healthy life style (avoidance of cigarettes, alcohol, drugs, stress or other triggers) and (nocturnal) supervision seem to be the actions that can be undertaken by the patient [5,6].

3. Seizure detection

The gold standard for seizure detection is video-EEG, with electrodes attached to the scalp or implanted in case of stereotactic EEG. Even though implantation could reduce EEG artifacts and intracranial systems are unobtrusive after the device is well in place, the risks of implanting cannot be ignored, and neither can the discomfort and stigmatization caused by head-attached devices for measurement of scalp EEG.

Furthermore, they raise a number of other questions as well.

What are the costs of implementing and maintaining seizure prediction devices [7,8]? Does EEG detect all seizures? Should EEG recordings be combined with physiological sources as a standard form, given that the difficulty of detecting seizures is exacerbated by contamination of EEG recordings with environmental and biological artifacts (especially in scalp EEG) [9]? Could a seizure indeed be aborted through medication administration or electrical stimulation after the onset of electrographic seizure activity, or has the brain already passed the 'point of no return', to a state that will inevitably progress into a clinical seizure manifestation [10]? Which actions should be taken and when, both for preventing seizures and for preventing SUDEP? Where in the brain should local medication administration or electrical stimulation be executed? Who would benefit from preventive measures? What is the damage of preventive measures for false positive detections? Do subclinical events require action? According Osorio and Manly [11] they are less severe than clinical seizures, but Boylan et al. [12] state that in neonates, they can be equally detrimental towards brain injury.

EEG based seizure detection is useful and even necessary in neonates that stay in the Neonatal Intensive Care Unit and that are known to have subtle seizures that are very similar to normal behavior in newborns: sustained eye opening with ocular fixation, repetitive blinking or fluttering of the eyelids, drooling, sucking and other slight facial manifestations. Furthermore, there is often an electro-clinical dissociation between EEG and clinical seizure, making it difficult to recognize an epileptic seizure even using video-EEG, and the majority of electrographic seizures do not produce clinical symptoms at all [12,13]. Even though their seizures are very subtle or without clinical signs, some researchers focus on video based detection [14,15]. Others focus on ECG (electrocardiography) based detection [9,16,17] or a combination of EEG and ECG [18].

Non-EEG sensing devices can be implanted as well, but they can also be non-invasive or even unobtrusive. They include remote sensors such as video or radar (requiring the patient to stay within a certain distance), other contactless sensing methods such as a sensor mattress or e-chair, and wearable technologies. The latter include three different systems. First, carry-on devices such as smart watches or e-accessories. Second, smart textiles such as t-shirts, gloves or socks with knitted electronic wires or optical fibers. They have already proven to be able to incorporate measurement of movement, heart rhythm, muscle tension, respiration, body position, temperature, blood pressure, oxygen saturation, electrodermal activity and patient location. Third, flexible-stretchable-printable electronics can even be printed directly on the human body as 'temporary tattoos' [19,20].

4. Detection systems

The following sections provide an overview of various non-EEG based seizure detection methods. The focus lies on non-invasive systems that can be used as an alarm system at the home (environment) of the patient. Detection by metabolic (including hormonal) or tissue stress biomarkers is not listed, as such devices are usually invasive, nor is NIRS (near-infrared spectroscopy), measuring cerebral perfusion and brain oxygenation, as with the currently available technology, this would require a head-mounted so quite obtrusive and stigmatizing device [21]. Seizure alert (predictor) and seizure response (detector) dogs are also outside the scope of this article. Evidence is conflicting [22] and they can only be used by adult patients who can train the dog and who have a minimum number of seizures per month to do so.

The discussed studies (published recently or in the past) only include those teams that developed both the detection device and the seizure algorithm, and tested the latter on real seizures in human, with comparison to video-EEG and disclosure of results. Table 1 therefore does not include studies that performed offline analysis of signals monitored as routine practice during video-EEG monitoring (such as video). Reported results of non-EEG based detection devices vary between 2.2% and 100% sensitivity and between 0 and 3.23 false detections per hour compared to the gold standard video-EEG, for seizures ranging from generalized seizures to convulsive or non-convulsive focal seizures with or without loss of consciousness.

4.1. Cardiovascular changes

4.1.1. Heart rhythm

Monitoring of heart rhythm can be done by ECG (electrocardiography), BCG (ballistocardiography), PPG (photoplethysmography) or

Table 1
Human studies involving non-EEG based seizure detection methods, including development of a device, as well as algorithms and their results. Below the bold line: articles on seizure alarm systems that are commercially available or under clinical trial investigation, further discussed in Table 3. 2r = secondarily generalized, A = automotor seizure, ACM = accelerometer, C = clonic seizure, CPS = complex partial seizure (now: focal seizure with loss of consciousness), ECG = electrocardiography, EDA = electrodermal activity, EEG = electroencephalography, EMG = electromyography, FDR = false detection rate, FLS = frontal lobe seizures, FP = false positive(s), (s)(G)TC(S) = (secondarily) (generalized) tonic–clonic seizure, gyro = gyroscope, h = hours, H = hyperkinetic frontal lobe seizure, HR = heart rate, IR = infrared wave, M = myoclonic seizure, magneto = magnetometer, μS = microsiemens, mvmt = movement, PNES = psychogenic non-epileptic seizures, PPG = photoplethysmography, PPV = positive predictive value (inversely proportional to FDR), S = spasms, sec = seconds, SIDS = sudden infant death syndrome, SpO_2 = blood oxygenation, SPS = simple partial (motor) seizure (now: focal seizure without loss of consciousness), T = tonic seizure, TLS = temporal lobe seizure, V = versive seizure.

Article	Team location	Detection method(s)	Test subjects	Seizure number + type if known	Real time (alarm)	Contact(less)	Results
Becq et al. [23]	France	ACM + magneto	2 patients	46 TC, C	Yes	Attached to torso/wrist	Sensitivity 90%, FDR per night 0.7
Borujeny et al. [24]	Iran	ACM	3 patients	20 unspecified seizures	Yes	Attached to arms & left thigh	Sensitivity 85%, 3 FP
Cogan et al. [25]	US	PPG for heart rhythm + SpO_2 + EDA (temperature & ACM not used)	5 patients	12 seizures (sGTCS & non-convulsive CPS)	No	Watch & finger cuff	Sensitivity 58%, FDR per hour 0.01
Conradsen et al. [26]	Denmark	ACM + gyro + EMG (integrated magneto not used)	10 healthy adults, 1 adult patient	Simulated M/V/TC, 1 real TC	No	Sensor suit + electrodes attached to belly/limbs	For different combinations of methods: see article, best results when combining all three: sensitivity 100%, FDR per hour 0, mean latency 0.75 s
Dalton et al. [27]	US/Ireland	ACM	5 adult patients	21 M, C	No	Attached to limbs	Sensitivity 91%, 50 FP (daytime) in 130 h
Gubbi et al. [28]	Australia	ACM	8 patients	14 unspecified seizures, 5 PNES	No	iPod Touch attached to wrists with elastic armbands	Sensitivity 100%, unspecified but few FP
Jallon [29]	France	ACM	2 patients	46 unspecified seizures	Yes	Attached to torso/wrist	Sensitivity 88–89%, PPV 55–75%, FDR 0.5–0.7 per night
Massé et al. [30], van Elmpt et al. [31]	Netherlands/ Belgium	ECG (integrated ACM not used)	17 patients (10 with seizures)	104 (mostly T and M but also absence and TC)	Yes (but not yet in article)	Necklace or attached to arm + electrodes on chest	HR changes in 50/104 (48%) of 8 patients, algorithm tested on 3 patients with >10 seizures with HR changes: sensitivity >90%, PPV >50%
Milosevic et al. [32]	Belgium	ACM (+EMG)	7 pediatric patients	31 TC seizures of which 22 > 10 s used	No	Attached to limbs	*Best result ACM*: sensitivity 86.36%, FDR 1.94 per 12 h, median latency 19.4 s; *EMG results*: sensitivity 81.82%, FDR 0.6 per 12 h, median latency 10.5 s; *Combination 2 ACM + 2 EMG*: sensitivity 90.91%, FDR 0.45 per 12 h, median latency 10.5 s
Nijsen et al. [33]	Netherlands	ACM	36 patients (18 with seizures)	27 T	No	Attached to arm	Sensitivity 80% (5 missed e.g., because movement was blocked), PPV 35% (42% of the false alarms being M or C)
Nijsen et al. [34]	Netherlands	ACM	15 patients for training, 21 for testing	29 M for training, 35 for testing	No	Attached to arms	Sensitivity 80%, PPV 16% (148 FP during 3.6 h, among which also C and T)
Schulc et al. [35]	Austria	ACM	20 adult patients (3 with seizures)	4 GTCS	Yes	Wii Remote attached to arm	Sensitivity 100%, PPV $\geq$ 75%

Table 1 (*Continued*)

Article	Team location	Detection method(s)	Test subjects	Seizure number + type if known	Real time (alarm)	Contact(less)	Results
van Andel et al. unpublished results [36]	Netherlands	ACM + ECG + video + audio	43 patients (23 with seizures)	86 TC, H, C, T, cluster of at least 5 T, M or S	No	ACM upper arms, ECG with 2 wired electrodes on chest connected to arm	*Using 4 modalities*: sensitivity 72%, FDR 5.2 per 8 h, mean latency 13 s; *Using ACM & ECG & only counting clinically urgent seizures*: sensitivity 87%, FDR 6.3 per 8 h (PPV 43%), mean latency 60 s
Van de Vel et al. [37]	Belgium	ACM	7 pediatric patients	51 H of which 2 per patient used	No	Attached to limbs	Sensitivity 95.71%, PPV 57.84% in 180 h
Beniczky et al. [38] Epi-Care Free	Denmark	ACM	73 pediatric and adult patients (20 with seizures)	39 GTCS	Yes	Bracelet	Sensitivity 89.7% (35/39, none of the 149 non-GTCS triggered an alarm), mean latency 55 s, FDR 0.2/day (40 FP, all during daytime tasks)
Carlson et al. [39] MP5	US	Audio	64 pediatric and adult patients	8 TC	Yes	Between bed and mattress	Sensitivity 63% (5 detected), PPV 3.3% (269 FP during 1528 h)
Conradsen et al. [40] Eddi	Denmark	EMG	5 patients (2 with seizures)	7 GTCS	Yes	Electrodes attached to leg	Mean sensitivity 57% (4/7), latency 25 s, FDR 0.003/h (1 FP)
Fulton et al. [41] ST-2/MP5	US	Audio (+surface pressure)	27 pediatric patients (15 with seizures)	9 TC + 8 2r TC + 10 CPS + 2 SPS + 40 M, T, M + T = 69	Yes	Between bed and mattress	MP5: detection rate 4.3% (1/23: a TC), ST-2: 2.2% (1/46: a CPS)
Kramer et al. [42] EpiLert	Israel	ACM	31 patients (15 with seizures)	22 T, C, TC	Yes	Watch-like	Sensitivity 91% (20 detected), 8 FP in 1692 h (FDR per 24 h 0.11, all daytime), median latency 17 s
Larsen et al. [43] Eddi	Denmark	EMG	6 patients	26 T	No	Electrodes attached to deltoids	Sensitivity 87.5%, FDR 3.23 per hour
Lockman et al. [44] SmartWatch	US	ACM	40 adult patients (6 with seizures)	8 TC	Yes	Watch	7/8 (87.5%) detected of which 2 during day, PPV >50% (204 FP during day when alarm can be turned off, 1 at night), latency to onset C phase 4–15 s
Narechania et al. [45] Emfit	US	ACM	51 adult patients (13 with seizures)	18 GTCS	Yes	Under mattress mat	Sensitivity 89% (100% during sleep), FDR 0.07 per 12 h (all during wake)
Patterson et al. [46] SmartWatch	US	ACM	41 pediatric & young adult patients	51 GTCS, 47 rhythmic arm mvmt = 191	Yes	Watch	Sensitivity all seizures 16%, GTCS 31%, rhythmic arm mvmt 34%, unspecified but high FDR
Poh et al. [47] Embrace	US	EDA + ACM	80 pediatric patients (7 with seizures)	16 GTCS	No	Wristband with electrodes	Sensitivity 94% (15/16), FDR per 24 h 0.74 (130 false alarms, mainly during day)
Sabesan and Sankar [48] ProGuardian	US	ECG + ACM	1. Unspecified 2. Pediatric patients	1. CPS 2. H	No	Chest worn patch	581 h ECG data of 1. taken & 540 h ACM data of 2. Overall sensitivity >80%, 2 FP per night

Szabó et al. [49] Brain Sentinel	US	EMG	33 adolescent & adult patients	21 GTCS	No	Electrodes attached to biceps	Sensitivity 95% (20/21, none of the other 175 seizures detected), 1 FP in 1399 h (day & night), average latency 20 s
Van Poppel et al. [50] Emfit	US	ACM	45 pediatric & young adult patients (26 with seizures)	16 GTCS, 7 simple motor, 12 motor CPS, 11 T, 12 M-T, 9 non-motor CPS, 11 M = 78 (28 in sleep)	Yes	Under mattress mat	Sensitivity 75% for GTCS in wake, 85% for GTCS in sleep, 30% for all seizures, 54% for all seizures in sleep

PCG (phonocardiography). ECG measures the electrical properties of the heart and even one or two-lead ECG can detect heart rate (HR), heart rate variability (HRV) as well as ECG morphology, the other methods only detect heart rate. BCG measures the micro movements of the torso caused by the pumping of blood. Plethysmography measures the volume within an organ which can be air in respiration measurement or blood in heart rate, blood pressure and oxygen saturation measurements. PPG does so optically by using a light source (LED) which emits infra-red or visible red light into the tissue and one or two photo-detectors (optical sensors) to collect light reflected from (e.g., when a watch is used) or transmitted through (for small body parts e.g., when a finger cuff is used) the tissue [20]. The lack of electrodes and wires reduces potential skin irritation, and there is less risk of losing the signal due to electrodes falling off; in case of bad contact with the skin (due to high-frequency motion or increased sweating), PPG can still measure the heart rate (possibly with a delay and with artifacts though) since it still has a reflecting surface [51,52]. Corruption of the PPG signal arises from influences of ambient light and motion, the latter which can be canceled by adding movement measurement, and PPG appears to be less sensitive to motion artifacts than ECG [52,53]. Finally, PCG measures the sound of the pulse as done by a stethoscope [19].

Persistent HR elevations after exercise, decreased HRV (changes in the heart's beat-to-beat interval reflecting autonomic nervous system activation; the bigger the variation, the more the body is able to react and adapt) and ECG morphology abnormalities (arrhythmic, conduction or repolarization abnormalities) are established predictors of sudden cardiac death in other medical conditions or in healthy populations [54].

Seizure-related HR changes commonly occur, and they are more pronounced with generalized tonic–clonic seizures (GTCS), hyperkinetic frontal lobe seizures (FLS) and temporal lobe seizures (TLS). They can be ictal tachycardia, bradycardia or in the worst case asystole, and the former often even occurs pre-ictally [55,56]. Such events subsequently increase the risk of SUDEP.

Epilepsy patients already have reduced HRV inter-ictally, and HRV has also proven to discriminate focal epileptic seizures from physical exercise [57]. Ponnusamy et al. [58] observed HRV differences (high sympathetic and low vagal tone) in TLS, as compared to psychogenic non-epileptic seizures.

An example of a change in ECG morphology is the QT interval shortening in GTCS, found by Surges et al. [54].

Challenges remain though and include the use of cardiac based detection for distinguishing arousal from sleep, standing from reclining and exercises (e.g., climbing stairs) from seizures. The combination with a chest accelerometer to determine position might already be a first step towards a possible solution.

A team from the Netherlands and Belgium and the partnership between Holst Center/imec and Hobo Heeze BV worked to develop a system that is attached to the chest and arm, which uses ECG for seizure detection. Published results and more information are mentioned in Table 1 [30,31]. The Netherlands team later evolved to a combination of ECG, ACM (accelerometer), video and audio based detection [36] (Table 1) then testing the Livassured NightWatch combining ACM and PPG based HR detection at the upper arm (Table 3 in §6 'Commercialized systems').

ECG is also incorporated in the RTI International (US) device and the Neuronaute smart textile by the French company Bioserenity (Table 3).

Table 3 further mentions that the commercially available bed-mounted seizure-detection system Emfit (Finnish company Emfit Ltd.) can detect seizures by BCG. This information was taken from its website, no publication could be found.

US company LivaNova developed both the ProGuardian system (using a chest worn patch for ECG and ACM based seizure detection) [48] and the CE and FDA approved AspireSR system

(using implanted ECG based detection with closed-loop vagal nerve stimulation or VNS) [59,60]. Only the former is mentioned in Tables 1 and 3 as we focus on non-implanted devices.

PPG is the method used to detect HR by many smart and fitness watches, and it is also incorporated in the wristwatch developed by the team of Cogan et al. [25] (Table 1), by the PulseGuard smart watch by UK company Adris Technologies (Table 3) and the Embrace by US company Empatica [47] (Tables 1 and 3).

4.1.2. Blood pressure

Blood pressure measurements can be performed by arm cuff based monitors or finger plethysmography which is included in pulse oximeters. The latter technique can detect heart rate, pulse wave amplitude and, in combination with ECG, pulse transit time. The latter is inversely correlated with blood pressure [19,61].

Drug-induced seizures in humans resulted in increases of 82 and 42 mmHg in mean systolic and diastolic pressures respectively, the peak being within a minute of seizure onset. Return to baseline follows within 60 min, even though SE (status epilepticus) may be ongoing [62].

4.1.3. Oxygen saturation

A pulse oximeter is a clamp attached to ear lobe or fingertip (which could be integrated into a ring or glove). For babies, it can be integrated into a foot strap or body sticker. It consists of a saturometer (which uses infrared waves to sense blood–oxygen concentration) and a plethysmograph. Cogan et al. [25] integrated it in their watch-connected finger cuff to combine it with heart rate measurement and EDA (electrodermal activity or perspiration monitoring) for seizure detection (Table 1). They found first heart rate, then oxygen saturation followed by EDA change during seizures. The advantage is the very stable signal and easy algorithm: a simple drop of the saturation percentage is needed to alert for seizures (in comparison, a 4% drop for minimum 8 s is defined for apnea).

4.2. Respiration changes

Respiration is frequently altered during seizures, and monitoring is also important in preventing SUDEP, not only for monitoring breathing and apnea, but for detecting sighs, yawns and arousal. Low arousability is a possible sign of near-SUDEP, and two important mechanisms involved in auto-resuscitation are arousal and gasping [63,64]. Numerous methods exist for monitoring respiration, including the sensing of airflow temperature, pressure or velocity; chest movement or volume changes; transcutaneous blood–oxygen concentration or partial pressure; respiratory gases oxygen or carbon dioxide concentration; transcutaneous audio or vibration signals resulting from breathing turbulence in the larynx; and even ECG.

A thermocouple or thermistor placed below the nose senses airflow temperature, a mask covering the nose and mouth senses airflow pressure and a pneumotachography mask senses airflow pressure or velocity. Although these devices are in common use, they are associated with several disadvantages, including their discomfort and influence on breathing [65].

Sensing chest and abdominal wall movement in order to measure respiratory rate, depth or effort is often performed by measuring volume differences between the upper and lower chest using two straps (respiratory inductance plethysmography or RIP [65]), two electrodes (impedance pneumography [66]) or magnetometers [65], although it can also be performed using a single EMG (electromyography, on diaphragm or intercostals muscles) or ACM sensor (on chest or bed), and even through remote measurement using video or microwaves. One disadvantage is that respiratory movements can continue when there is already apnea. As mentioned in Table 3, the commercially available bed-mounted seizure-detection systems Ep-It P139 (UK company Alert-It), Aremco (UK company Aremco) and Emfit (Emfit Ltd.) can detect respiration changes by monitoring movement. RTI International uses a torso band to measure respiration in combination with other signals. This information was again taken from their websites, no publications could be found.

Oximetry is important, as it can identify rises in blood pressure due to airway blockage (e.g., because of prone position), despite continuing misleading respiratory movements. The complex interaction between brain, heart and respiration makes data on oxygenation crucial in addition to information on respiration and heart rhythm [64,67].

Electrodes that sense the transcutaneous partial pressure of oxygen can detect respiration abnormalities faster and with fewer false positives than saturometers (oximeters) produce. Poets [64] has searched for possible mechanisms of Sudden Infant Death Syndrome by measuring different respiration parameters. In this study, electrodes were combined with pulse oximetry and chest movement detection, with the following findings: decreased pressure without decreased saturation indicates changes in skin perfusion, but not arterial hypoxemia; decreases in both pressure and saturation accompanied by tachycardia and slower, irregular or absent respiration indicate an epileptic seizure; and decreases in both pressure and saturation, preceded by increased amplitude and irregular breathing movement (often combined with tachycardia and massive body movements) indicate suffocation.

Oxygraphy and capnography monitor the concentration (using infrared waves, as in pulse oximetry) or partial pressure (using electrodes, as above) of oxygen and carbon dioxide in respiratory gases [68].

A miniature device attached to the skin of the suprasternal notch on the neck can measure airflow by detecting sound created by turbulence occurring in the human respiratory system. Such a device is manufactured by the UK company Ervitech. Although it is assumed to detect apnea during seizures, the articles published to date do not focus on epilepsy yet [69].

Finally, ECG-derived respiration (EDR) is an option, as respiration alters the ECG signal by changing electrical impedance due to volume changes in the lungs. The changing position of the electrodes with respect to the heart, change the morphology of the ECG signal. Even in some seizures without big cardiac changes, decoupling of heart rhythm and respiration is seen, which can be measured using EDR. Respiration is a very slow signal though, and seizures often have a very variable and short duration, which is why more studies focus on cardiac than respiration based detection [70].

4.3. Other autonomic changes: electrodermal activity

Autonomic changes can affect the skin in three different ways. Skin perfusion, manifested by flushing, can be measured with electrodes. For goose bumps/piloerection, forms of detection other than by video or self-reporting have not been described [71]. EDA, defined as skin resistance or conductance, is measured by ohmmeters or galvanometers respectively and shows as sweating/sudomotor signs.

GTCS show an increase in autonomic discharges, particularly sympathetic. While changes in blood pressure, HR(V), respiration and other autonomic signs are controlled by both the parasympaticus and the orthosympaticus, sweat glands are surrounded by sympathetic fibers. Modulation in EDA thus reflects purely sympathetic activity and could be used for GTCS detection, but EDA changes are detected slower than heart rate changes according to Cogan et al. [25].

One US team has published a report on a wrist-attached device (Embrace by Empatica) that combines EDA and ACM (the watch

also measures temperature and heart rate by PPG) in order to detect seizures (Tables 1 and 3) [47]. Also the research group of Cogan et al. [25] incorporates EDA in their watch as previously mentioned. Both groups are the only ones claiming their device can detect non-convulsive focal seizures with loss of consciousness (former complex partial seizures). The results of Cogan are quite weak though, and Empatica has not yet scientifically proven its statement.

4.4. Motor activity

4.4.1. Video

Video detection is part of the gold standard for seizure detection, and it is the only means of performing retroactive visual evaluation of detected events. It is contactless, unless infrared wave reflectors are affixed to motion-relevant locations on the patient's body (e.g., joints or extremities) [72]. Video might even be used to detect HR(V) and respiration rate [73,74].

One disadvantage of video detection involves the difficulty of detecting movement under blankets (although shapes on the blanket help) or the need to sleep without a blanket when using coloured pyjamas [75]. Further, recording all aspects of a movement requires the patient to be constantly within the scope of one or more cameras (this is less problematic at night).

A thermal or thermographic camera detecting infrared waves from body (movement) through blankets and clothing could also be used. Such cameras are also assumed able to detect respiration and heart rate [76,77]. Disadvantages involve the current reliability of such cameras (the resolution is considerably inferior to that of optical cameras), and their cost.

The biggest disadvantage of video based detection is obviously the privacy issue, although the transmitted data can be the alerts or processed signals only, the images do not necessarily need to be included.

Teams from Belgium, the US, Germany/Portugal and Italy are independently focusing on seizure detection using automated video analysis [14,15,72,78]. SAMi Alert by US company SAMi can be used for convulsive seizure detection. An iPhone or iPad needs to be used to display the video and raise alarms (Table 3).

4.4.2. Electromagnetic waves

Using the Doppler effect, microwaves and radio waves have been tested for detecting movement, as well as heart rate and respiration, and temperature [20,79,80]. Infrared motion sensors have been tested for detection of nocturnal seizures by Shankar et al. [81].

Such techniques offer the advantage of allowing contactless recording through blankets and clothing. Disadvantages of electromagnetic devices involve their current reliability and the constant electromagnetic radiation exposure. Radiation damage depends upon the wave type (some have ionizing – not the radio, infrared or microwaves –, electrical or biological/heating effects on the human body), intensity, cumulative exposure and exposure duration.

4.4.3. Accelerometer, gyroscope and magnetometer

ACM devices measure translational acceleration. They have a low cost and with their low energy consumption, they enable ambulatory monitoring with a small device which has a large storage capacity, a fast processing speed and allows addition of many features. They are used in many medical applications for activity recognition. For example in Parkinson's disease, they are used to distinguish normal movements from hypokinesia, bradykinesia or dyskinesia [24]. They can be used for detecting clonic seizures [44].

Gyro sensors measure angular/rotational acceleration and are useful for detecting versive seizures. They consume more energy than ACM devices. Magneto sensors can determine position and orientation changes of limbs or body and are interesting for detecting tonic seizures, because of the 'positioning' that takes place in these seizures. They are thus also useful for detecting tonic–clonic seizures because of their capacity to detect the tonic phase, early into the seizure [23]. They are sensitive to some environmental factors though, and obviously influenced by an external magnetic field.

Attached to the patient, these sensors have the advantage of being linked directly to movement (including motor seizures) and of being able to distinguish between the movements of individual limbs, however if only one ACM sensor is used, it needs to be attached to the proper limb that is always involved in the patient's (motor) seizures. Attached to the bed or mattress, they are more comfortable for the patient and possibly less susceptible to dislocation over time.

Several teams from Australia, Austria, Belgium, Denmark, France, Iran, Israel, the Netherlands, the US and US/Ireland are performing research on movement detection using one or a combination of ACM, gyro and magneto, a combination with another detection method, or have tested a commercially available device. The results of their research are mentioned in Table 1. ACM is the method used to detect movement by many smart and fitness watches, and many commercially available seizure detection systems use this or an unspecified movement-detection method. See Table 3 for more information.

4.4.4. Electromyography

Because they record muscle signals, EMG devices are well suited for detecting tonic seizures and the early phase of tonic–clonic seizures [40].

They have the same (dis)advantages as other sensors attached to the patient.

Table 1 mentions research by a team in Denmark [26,40,43] and in the US [49] and also our own team developed algorithms for EMG but not a corresponding device, routine EMG recorded during video-EEG was analyzed [32]. In contrast, the team of Conradsen and Larsen developed and tested (on leg versus deltoid muscle, the latter giving better results) Eddi by Danish company IctalCare A/S and Szabó et al. the US company Brain Sentinel device attached to biceps (Table 3).

4.5. Audio

Noises that occur during seizures include stereotypical screams, singing or humming, autonomic laughing or weeping, bronchial secretions, lip smacking and bed noises when moving. In addition and as mentioned, some audio devices can even detect respiration.

The advantages of audio devices include their low cost, comfort (contactless) and practical use, which is why, to date, they are the most commonly used system for pediatric patients in the form of rattling bracelets or based on baby monitor systems.

One disadvantage of audio devices involves their generally poor performance and detection of many false positives. One major challenge to this technique involves the development of algorithms that can suppress background noises originating from the environment, as well as from the patient such as speech or snoring. In some cases, however, snoring can be a seizure manifestation. For example tonic–clonic seizures are often followed by loud and typically stertorous breathing [82].

Various audio systems produced by the UK company Medpage have undergone testing by US research teams. Results and more information can be found in Tables 1 and 3 [39,41]. Table 1 also

shows research results regarding audio based seizure detection in combination with other methods, conducted by a team from the Netherlands [36]. Table 3 further lists Aremco (Aremco), Ep-It (UK company Alert-It) and SAMi (SAMi Alert) systems that combine audio with other detection methods, but for which no publications could be found.

4.6. Eye movements

Both eyelid and ocular movements can be detected by electro-oculography (EOG), which is capable of differentiating epileptic seizures from syncope, psychogenic or other non-epileptic seizures [83]. The Epicall system by Israeli company Epicall Ltd. uses a sticker placed on the side of the face to measure eye movements, heart rate and pulse as pre-seizure or early seizure markers. No clinical trial results have been published yet.

4.7. Temperature changes

It remains to be investigated whether temperature measurement can detect seizures. Although it would be an appropriate method for detecting febrile seizures, the exact relationship of these seizures to epilepsy is often not known. Temperature changes can be measured by thermometers that exist in the form of adhesive stickers or probes in watches, by radiometers and by thermal cameras that additionally could detect movement [19]. Measurement of temperature changes in exhaled air is discussed in Section 4.2.

Temperature sensing is included in the Empatica and RTI International devices (Table 3).

4.8. Body/surface pressure changes

Pressure mats can be used to detect bed vacancy (falling or somnambulism), although they are not designed specifically as a method for detecting seizures. These mats can be combined with other detection modalities, as is the case with some commercially available seizure-detection devices, including Ep-It (Alert-It), Aremco (Aremco), Emfit (Emfit Ltd.) and ST-2 (Medpage) (Table 3).

4.9. Moisture

In addition to the measurement of sweating, humidity meters can detect ictal symptoms including salivation, vomiting and incontinence. One disadvantage is that such manifestations are not related exclusively to seizures. Some commercial seizure-detection systems, however, including Sensalert (UK company Sensorium), Aremco (Aremco) and Ep-It (Alert-It), make use of a sheet with sensor wires sewn into silver in order to combine moisture sensing with other detection methods.

5. Multimodal

Some published studies, including those reported by a team in Denmark [26] and in France [23,29,84] have already combined several methods for movement detection. Studies by teams in the US [25] and the Netherlands [36] and some commercial devices even combine methods for detecting multiple body signals. There can be composition of signals and sensors that each try to detect

Table 2
Non-EEG seizure manifestations and corresponding detection methods. ACM = accelerometer, BP = blood pressure, ECG = electrocardiography, EDR = ECG-derived respiration, EMG = electromyography, EOG = electro-oculography, gyro = gyroscope, HR = heart rhythm, magneto = magnetometer, PCG = phonocardiography, pO_2/CO_2 = partial pressure oxygen/carbon dioxide, PPG = photoplethysmography, RIP = Respiratory Inductance Plethysmography, SpO_2 = blood oxygenation.

			DETECTION METHODS							
			Audio	**Video**	**Electro-magnetic waves**	**ACM/ gyro/ magneto**	**Electrodes**	**Plethys-mograph (volume)**	**Pressure**	**Tempe-rature**
NON-EEG SEIZURE MANIFESTATIONS	Motor	Body	bed noise	optical or thermal camera	radio, infrared or microwaves	bed or body attached	EMG		pressure mat for bed vacancy	
		Eye(lid)		optical camera			EOG/EMG			
	Auto-nomic	HR	PCG	thermal camera	radio or microwaves (BCG)	BCG	ECG	PPG		
		BP						PPG		
		SpO_2			infrared waves of oximeter					
		Respira-tion	neck	thermal camera	radio or microwaves chest, infrared waves of oximeter/ capnograph	ACM/ magneto chest	EMG, EDR, impedance pneumograph chest, electrodes for pO_2/CO_2	RIP chest	pneumo-tachograph airflow	thermo-couple airflow
		Sweating					ohm/ galvanometer			
		Vomiting/ salivation/ coughing	audio phone				humidity meter			
		Inconti-nence					humidity meter			
	Vocalizations		audio phone							
	Fever			thermal camera	radio waves					sticker

Table 3
Non-EEG alarm systems that are commercially available or under clinical trial investigation and that are specifically aimed at epilepsy and epileptic seizures. Information given as available in article or on website. ACM = accelerometer, C = clonic seizures, CPS = complex partial seizures (now: focal seizures with loss of consciousness), ECG = electrocardiography, EMG = electromyography, EOG = electro-oculography, H = hyperkinetic frontal lobe seizures, Hz = hertz, M = myoclonic seizures, npf = no publication found with our search strategy, PPG = photoplethysmography, S = spasms, sec = seconds, T = tonic seizures, TC = tonic–clonic seizures, VNS = vagal nerve stimulation.

Company	Device name	Detection method	Contact(less)	Seizures/events	Article	Website
Adris Technologies (UK)	**PulseGuard**	PPG for heart rhythm	Watch coupled to iPad	Unspecified	npf	http://www.pulseguard.org
Alert-It (UK)	**Ep-It Companion Monitor (S1029)**	Unspecified movement sensor, audio, moisture sensor, surface pressure	Under mattress (mat) and on mattress or under pillow sheet	TC and S, urination and vomiting, prolonged bed vacancy	npf	http://www.alert-it.co.uk
	Ep-It Guardian Monitor (P139)	Unspecified movement sensor that can also detect respiration, audio, moisture sensor, surface pressure	Under mattress (mat) and on mattress or under pillow sheet	TC, S and complex seizures, abnormal breathing, urination and vomiting, prolonged bed vacancy, allows monitoring of up to 32 patients	npf	
Aremco (UK)	**Aremco**	Respiration, audio, moisture, surface pressure	Under mattress plate	S	npf	http://www.disabilityworld.com/co/company.php?ID=3460
BioLert (Israel)	**EpiLert**	ACM for movement	Watch-like	TC, T, C	Kramer et al. [42]	http://www.biolertsys.com
Bioserenity (France)	**Neuronaute**	Unspecified sensors (ECG?, ACM?), EEG	Smart t-shirt & cap (the latter for EEG) coupled to smart phone	Unspecified	npf	http://www.bioserenity.com
Brain Sentinel (US)	**Brain Sentinel**	EMG	Device worn with strap on biceps	TC	Szabó et al. [49]	https://www.brainsentinel.com
Danish Care (Denmark)	**Epi-Care Free**	ACM for movement	Bracelet	TC in adults and teenagers	Beniczky et al. [38]	http://danishcare.dk/dk
	Epi-Care 3000	ACM for movement	Affixed to mattress	Convulsions such as TC, S mainly in small children	npf	
D.C.T. Associates Pty Ltd. (Australia)	**Vigil-Aide**	Unspecified vibration detection	Affixed to bed or worn in pouch/belt during day	Convulsions	npf	http://www.dctassociates.com.au/convul.htm
Emfit Ltd. (Finland)	**Emfit Seizure Monitor**	ACM for movement and respiration (even heart beating according to website), surface pressure	Under mattress mat	Convulsions such as TC and S, micro movements caused by breathing and heart beating, prolonged bed vacancy	Narechania et al. [45], Van Poppel et al. [50]	http://www.emfit.com
Empatica (US)	**Embrace**	PPG for heart rhythm, EDA, temperature, ACM	Watch coupled to smart phone	TC, non-convulsive seizures such as CPS	Poh et al. [47]	https://www.empatica.com/embrace-watch-epilepsy-monitor
IctalCare A/S (Denmark)	**Eddi**	EMG	ePatch attached to upper arm or leg	TC, T	Conradsen et al. [40], Larsen et al. [43]	http://www.ictalcare.dk
LivaNova (former Cyberonics, US)	**ProGuardian**	ECG + ACM	Chest worn patch & bedside hub	CPS, H	Sabesan et Sankar [48]	http://ir.livanova.cyberonics.com/releasedetail.cfm?releaseid=728198
Livassured (Netherlands)	**NightWatch**	PPG for heart rhythm + ACM	(Upper) arm band	Nocturnal TC	npf	http://www.livassured.nl
Medpage (UK)	**MP5**	Audio for movement (bed noises) and vocalizations, movement sensor	Under mattress	TC in patients weighing $\geq$12.7 kg	Carlson et al. [39],	http://www.medpage-ltd.com

Table 3 (*Continued*)

Company	Device name	Detection method	Contact(less)	Seizures/events	Article	Website
	ST-2 (out-dated)	Unspecified movement sensor (audio?) and surface pressure	Under mattress mat	TC & prolonged bed vacancy in patients weighing ≥12.7 kg	Fulton et al. [41] Fulton et al. [41]	
RTI International (US)	**RTI**	ECG, respiration, temperature, body orientation, EDA, (EMG)	Torso band & bracelet (the latter for EDA)	TC (to a lesser extent T & M)	npf	http://www.rti.org/newsroom/news.cfm?obj=5C9D1803-AE4A-EE86-583510843319AA948
SAMi Alert (US)	**SAMi**	Video based movement detection, audio	Camera coupled to iPhone or iPad	Unspecified nocturnal motor seizures	npf	http://www.samialert.com
Sensorium (UK)	**Sensalert (200/SPTX-EP200)**	Unspecified movement sensor and optional moisture sensor	Under mattress	TC	npf	http://www.sensorium.co.uk
Smart Monitor Corp. (US)	**SmartWatch**	ACM for movement	Watch coupled to Android smart phone	Convulsive seizures mainly TC, C	Lockman et al. [44], Patterson et al. [46]	http://www.smart-monitor.com
Vahlkamp (Netherlands)	**Epi-Watcher**	Unspecified movement sensor	Under mattress mat	TC	npf	http://www.vahlkamp.nl

the seizure, or there can be integration of signals to come to seizure detection.

Table 2 provides a summary of the seizure manifestations and corresponding detection methods that have been discussed and proposes possible combinations.

6. Commercialized systems

In this section (and in Table 3), the focus is on systems that are commercially available or under clinical trial investigation and that are specifically aimed at epilepsy and seizure detection. As mentioned, published, prospective studies are rare, and additional investigation is needed in order to provide neurologists and patients with an objective overview of advantages, disadvantages and efficacy of these systems.

One team from Memphis studied different commercially available devices such as the Emfit under mattress mat by Emfit Ltd. [50], the under mattress MP5 and ST-2 by Medpage [41] and SmartWatch by US company Smart Monitor Corporation [46]. They obtained (far) worse results i.e., a sensitivity of 4.3% for MP5 while Carlson et al. [39] reported 63%, a sensitivity of 75% for Emfit while Narechania et al. [45] reported 89%, and a sensitivity of 31% for SmartWatch while company-funded Lockman et al. [44] reported 87.5%.

Other literature reporting on marketed devices (listed below the bold line in Table 1 and in column 6 of Table 3) include that on the EMG based ePatch Eddi by IctalCare A/S [40,43], the Epi-Care Free bracelet by Danish company Danish Care [38], the EMG based Brain Sentinel device [49], the Embrace bracelet by Empatica [47], the ProGuardian chest patch by LivaNova [48] and the watch-like EpiLert by Israeli company BioLert [42].

All but the Medpage and Emfit Ltd. devices can be used during the day/outside of bed, and have shown results for tonic–clonic seizures ranging from 31% to 95% correct detections and <0.01 to 0.03 false detections per hour. Latency from clinical seizure onset to detection has been mentioned for some and range from 25 to 55 s. The majority of seizures were detected relatively late, as the devices are based on accelerometry, thus mainly identifying the clonic phase.

Other mobile device are the belt-worn or pouch-worn Vigil-Aide by D.C.T. Associates Pty Ltd. (Australia), which has a maximal range of 150 m (as compared to 20 m for the Epi-Care Free); the PulseGuard watch by Adris Technologies that connects with an iPad, so as long as there is internet connection, the range is unlimited; the Neuronaute smart t-shirt by Bioserenity; and the upper arm worn NightWatch by Livassured. No results have been published yet.

Visibility (or non-visibility) towards other people is important to consider for devices that are worn during the daytime.

Sensors attached under the mattress or bed are the most widespread, although they often lack specificity, detecting not only seizure but also normal movements [84]. They are not mobile and are therefore used primarily for detecting nocturnal seizures. In addition to the already mentioned, they include the Aremco plate, Epi-Care 3000 by Danish Care, Sensalert (200 and SPTX-EP200) by Sensorium, Epi-Watcher by Vahlkamp (Netherlands) and Ep-It (S1029 and P139) by Alert-It. Finally, the SAMi Alert camera by SAMi is a camera so not attached to bed or patient, but obviously the patient needs to stay within the scope of the camera.

Some devices have additional valuable features: canceling alerts that are set off inadvertently (SmartWatch); notifying a missed seizure using a push button (SmartWatch); adjusting patient-specific parameters, including threshold for seizure intensity (MP5, SmartWatch), seizure duration (SmartWatch), user weight (Sensalert), mattress type (MP5, Sensalert) and seizure nature (Sensalert); warning with a pre-alarm buzz or panic button

(Sensalert, SmartWatch); setting the alarm delay at different interval times (Vigil-Aide, Emfit); alerting the caregiver of the patient's position through an incorporated GPS (Eddi, EpiLert, SmartWatch); recording a log of the detected seizures with time and duration (Epi-Watcher, Epi-Care) and even movement pattern (SmartWatch); or they are/will be automatically coupled to an electronic seizure diary in the future (SmartWatch).

Device prices are not mentioned as these are susceptible to change,but the buyer should inform upfront about costs, as prices depend on the chosen device composites and options, and for example SmartMonitor Corporation works with a monthly subscription fee.

7. Applications for smart devices

As mentioned, the boom of smart phones and tablets has created a new market for development of seizure detection applications. Some applications (EpDetect for Android and Microsoft phones and EpilepsyApp for Android and iOS phones) use the phone itself to detect abnormal movement but this means the device has to be worn on the body e.g., in a pocket which decreases sensitivity, and the device might break during the seizure, disabling alerting a caregiver by sending out a text message or phone call. In most cases the smart phone needs to be coupled with widely available fitness or smart watches that are attached to the wrist and detect movement and/or heart rate, and both need installation of the application (Table 4). The previously mentioned SmartWatch, PulseGuard, Embrace and SAMi also work with apps, but as the watches (and camera for SAMi) were developed by the same company as the apps, these are also mentioned in the previous subsection. Obviously, a good internet connection is a requisite for proper functioning.

8. Discussion

Next to epilepsy treatment, epilepsy management becomes more and more important. This review gives an overview of body signals and methods for (ongoing) seizure detection, international research and (commercially) available systems and applications. Detecting seizures makes it possible to alert the caregiver. Injuries might not be completely preventable as the seizure has already started, but if a seizure can be detected early in its course, the patient might be kept from further injuries. Also, by seizure detection, injuries during post-ictal confusional wandering could be prevented. As injuries mainly occur due to intense movement or fall, it is particularly interesting to monitor motor signs. Epileptic patient supervision is also considered important for SUDEP risk reduction, both by alarming in case of seizures as by helping to understand the underlying (autonomic) mechanisms. The latter is why it is particularly interesting to include monitoring cardiac, respiratory or other autonomic dysfunction as these are possible pathophysiological mechanisms of SUDEP.

As in intracerebral devices or the implanted AspireSR system, also extracerebral devices could be coupled to an intervention to obtain a closed-loop device. This includes for example responsive stimulation of heart, respiration or muscles (including diaphragmatic pacing), administration of medication or oxygen, or (less obviously) the inflation of an 'airbag' to prevent injury. It seems obvious though, that when users are looking for a non-invasive alarm system, the coupled intervention (if requested) should be non-invasive as well.

Extracerebral or non-EEG based seizure detection is increasingly and internationally researched the last ten years but still, no reliable product has appeared on the market. There are clearly many obstacles in seizure detection research. Which events need to be detected? Is there a difference in daytime versus nighttime monitoring? Do seizures vary much between and within patients? These questions are discussed in the previous review article [3]. But also: how much data is needed to train a seizure detection algorithm? And which (practical) features should the system incorporate?

The collection of data is a tedious process with slow progress due to the small number of recorded seizures within a large amount of normal data. Furthermore, data annotation is a laborious and expensive task. Together with the argument that seizures change over time within one and the same patient, it leads us to promote a combination of novelty detection [85] and active learning [86], allowing a seizure detection device to go from patient-independent to patient-specific while already using it. Adapting to patient characteristics and seizures can also be done by the use of a modular design of the device, allowing the addition or removal of sensors or modalities.

To assess the need for seizure detection devices as well as requirements, it is important to incorporate user views into the development process, and to assess the device not only towards efficacy, but also towards comfort, user friendliness and therapeutic and social impact.

Table 4
Seizure detection applications for smart devices. HR = heart rate, OS = operating system.

Using	Application	Smart device and OS	Website
Smart phone only	EpDetect	Android or Microsoft phone	http://www.epdetect.com
	EpilepsyApp	Android or iOS phone	https://epilepsyapp.wordpress.com
Pebble watch detecting movement	Open Seizure Detector	Android phone	http://www.openseizuredetector.org.uk/?page_id=415
	Pebilepsy	Android phone	http://www.medgadget.com/2014/09/pebilepsy-uses-fitness-tracker-to-monitor-night-time-seizures.html
SmartWatch detecting movement	SmartWatch	Android or iOS phone	http://www.smart-monitor.com
MIO Alpha watch detecting HR	EpSyDet	Android phone	http://www.salvasoftware.com/epsydet
PulseGuard detecting HR	PulseGuard	iOS tablet (iPad)	http://www.pulseguard.org
Apple watch detecting movement and HR	EpiWatch	iOS phone (iPhone)	http://www.hopkinsmedicine.org/epiwatch#.VlTQm62FP4g
	SeizAlarm	iOS phone (iPhone)	http://www.seizalarm.com
Any watch detecting movement and/or HR	Neutun	Android or iOS phone	http://neutun.com
Embrace detecting movement, HR, EDA and temperature	EmpaticaAlert	Android or iOS phone	https://www.empatica.com/embrace-watch-epilepsy-monitor
SAMi camera detecting movement and sound	SAMi	iOS phone (iPhone) or tablet (iPad)	http://www.samialert.com

Many research group and companies have tested or developed a seizure detection device and published results. Comparison of results is difficult though as studies focus on different seizure types, timing (night versus day) and patients (adult versus pediatric patients). Results are also reported in different ways: some do not mention the test period making it impossible to calculate False Detection Rate, and few mention the latency between seizure and alarm. Two research groups have recently attempted to compare different studies that are also mentioned in this review article. van Andel et al. [87] mention a large variation in sensitivity and false detection rate for GTCS only, and disappointing results for other seizure types, and Jory et al. [88] warn for careful interpretation of results as studies are sometimes carried out by the team that developed the device or are sponsored by the manufacturer.

Nevertheless, we are convinced that the most effective seizure detection systems are multimodal, combining for example detection methods for movement and heart rate, which will be the focus of our future research.

9. Conclusion

Next to epilepsy treatment (cure), there is need for epilepsy management (care). Non-EEG based seizure detection is increasingly researched and can enhance quality of life of patient and caregiver by improving the quality of care, peace of mind and independence. This review gives an overview of body signals and methods for seizure detection, international research and (commercially) available systems and applications. We are convinced that a seizure detection device should be multimodal including monitoring of motor and autonomic signals, and that device and algorithm can be suboptimal at purchase, as long as it is able to 'adapt' to the patient's characteristics and seizures as well as to the user's wishes.

Conflict of interest statement

LivaNova (former Cyberonics) has paid the first author's salary until March 2014. The review article mentions the results of their ProGuardian device (as published by Sabesan et Sankar, 2015) objectively though and does not compare to other studies. In other words our work has not been influenced by the company.

References

[1] Mormann F, Elger CE, Lehnertz K. Seizure anticipation: from algorithms to clinical practice. Curr Opin Neurol 2006;19(2):187–93.
[2] Nijsen T, Arends J, Griep P, Cluitmans P. The potential value of three-dimensional accelerometry for detection of motor seizures in severe epilepsy. Epilepsy Behav 2005;7(1):74–84.
[3] Van de Vel A, Cuppens K, Bonroy B, Milosevic M, Jansen K, Van Huffel S, et al. Non-EEG seizure-detection systems and potential SUDEP prevention: state of the art. Seizure 2013;22:345–55.
[4] Samson K. Wearing the Detectives: wristbands, smartwatches, and other wearable devices allow for more real-time monitoring of seizures and other neurologic symptoms—and, possibly, more precise treatment. Neurol Now 2015;11(4):34–6.
[5] Ryvlin P, Nashef L, Tomson T. Prevention of sudden unexpected death in epilepsy: a realistic goal? Epilepsia 2013;54(Suppl. 2):23–8.
[6] Verma A, Kumar A. Sudden unexpected death in epilepsy: some approaches for its prevention and medico-legal consideration. Acta Neurol Belg 2015;115 (September (3)):207–12.
[7] Arthurs S, Zaveri HP, Frei MG, Osorio I. Patient and caregiver perspectives on seizure prediction. Epilepsy Behav 2010;19(3):474–7.
[8] Osorio I, Manly BFJ. Probability of detection of clinical seizures using heart rate changes. Seizure 2015;30:120–3.
[9] Malarvili MB, Mesbah M. Newborn seizure detection based on heart rate variability. IEEE Trans Biomed Eng 2009;56(11):2594–603.
[10] Mormann F, Andrzejak RG, Elger CE, Lehnertz K. Seizure prediction: the long and winding road. Brain 2007;130(Pt. 2):314–33.
[11] Osorio I, Manly BF. Is seizure detection based on EKG clinically relevant? Clin Neurophysiol 2014;125(10):1946–51.
[12] Boylan GB, Stevenson NJ, Vanhatalo S. Monitoring neonatal seizures. Semin Fetal Neonatal Med 2013;18(4):202–8.
[13] Yamamoto H, Okumura A, Fukuda M. Epilepsies and epileptic syndromes starting in the neonatal period. Brain Dev 2011;33(3):213–20.
[14] Karayiannis NB, Xiong Y, Tao G, Frost Jr. JD, Wise MS, Hrachovy RA, et al. Automated detection of videotaped neonatal seizures of epileptic origin. Epilepsia 2006;47(6):966–80.
[15] Ntonfo GMK, Ferrari G, Raheli R, Pisani F. Low-complexity image processing for real-time detection of neonatal clonic seizures. IEEE Trans Inf Technol Biomed 2012;16(3):375–82.
[16] Doyle OM, Temko A, Marnane W, Lightbody G, Boylan GB. Heart rate based automatic seizure detection in the newborn. Med Eng Phys 2010;32(8):829–39.
[17] Greene BR, Boylan GB, Reilly RB, de Chazal P, Connolly S. Combination of EEG and ECG for improved automatic neonatal seizure detection. Clin Neurophysiol 2007;118(6):1348–59.
[18] Greene BR, de Chazal P, Boylan GB, Connolly S, Reilly RB. Electrocardiogram based neonatal seizure detection. IEEE Trans Biomed Eng 2007;54(4):673–82.
[19] Pantelopoulos A, Bourbakis NG. A survey on wearable sensor-based systems for health monitoring and prognosis. IEEE Trans Syst Man Cyber 2010;40(1):1–12.
[20] Zheng Y-L, Ding X-R, Chung Yan Poon C, Ping Lai Lo B, Zhang H, Zhou X-L, et al. Unobtrusive sensing and wearable devices for health informatics. IEEE Trans Biomed Eng 2014;61(5):1538–54.
[21] Jeppesen J, Beniczky S, Johansen P, Sidenius P, Fuglsang-Frederiksen A. Exploring the capability of wireless near infrared spectroscopy as a portable seizure detection device for epilepsy patients. Seizure 2015;26:43–8.
[22] Ramgopal S, Thome-Souza S, Jackson M, Kadish NE, Sánchez Fernández I, Klehm J, et al. Seizure detection, seizure prediction, and closed-loop warning systems in epilepsy. Epilepsy Behav 2014;37C:291–307.
[23] Becq G, Bonnet S, Minotti L, Antonakios M, Guillemaud R, Kahane P. Classification of epileptic motor manifestations using inertial and magnetic sensors. Comput Biol Med 2011;41(1):46–55.
[24] Borujeny GT, Yazdi M, Keshavarz-Haddad A, Borujeny AR. Detection of epileptic seizure using wireless sensor networks. J Med Signals Sens 2013;3 (2):63–8.
[25] Cogan D, Nourani M, Harvey J, Nagaraddi V. Epileptic seizure detection using wristworn biosensors. Conf Proc IEEE Eng Med Biol Soc 2015;5086–9.
[26] Conradsen I, Beniczky S, Wolf P, Kjaer TW, Sams T, Sorensen HB. Automatic multi-modal intelligent seizure acquisition (MISA) system for detection of motor seizures from electromyographic data and motion data. Comput Methods Programs Biomed 2012;107(2):97–110.
[27] Dalton A, Patel S, Chowdhury A, Welsh M, Pang T, Schachter S, et al. Development of a body sensor network to detect motor patterns of epileptic seizures. IEEE Trans Biomed Eng 2012;59(11):3204–11.
[28] Gubbi J, Kusmakar S, Rao AS, Yan B, O'Brien TJ, Palaniswami M. Automatic detection and classification of convulsive psychogenic non-epileptic seizures using a wearable device. IEEE J Biomed Health Inform 2015(June) [Epub ahead of print].
[29] Jallon P. A Bayesian approach for epileptic seizures detection with 3D accelerometers. Conf Proc IEEE Eng Med Biol Soc 2010;6325–8.
[30] Massé F, Penders J, Sereteyn A, van Bussel M, Arends J. Miniaturized wireless ECG-monitor for real-time detection of epileptic seizures. Proc Wirel Health 2010;11:1–7.
[31] van Elmpt WJC, Nijsen TME, Griep PAM, Arends JBAM. A model of heart rate changes to detect seizures in severe epilepsy. Seizure 2006;15(6):366–75.
[32] Milosevic M, Van de Vel A, Bonroy B, Ceulemans B, Lagae L, Vanrumste B, et al. Automated detection of tonic-clonic seizures using 3D Accelerometry and surface electromyography in pediatric patients. IEEE J Biomed Health Inform 2015(July) [Epub ahead of print].
[33] Nijsen TME, Aarts RM, Arends JBAM, Cluitmans PJM. Automated detection of tonic seizures using 3-D accelerometry. IFMBE Proc 2008;22:188–91.
[34] Nijsen TME, Aarts RM, Cluitmans PJM, Griep PAM. Time-frequency analysis of accelerometry data for detection of myoclonic seizures. IEEE Trans Inf Technol Biomed 2010;14(5):1197–203.
[35] Schulc E, Unterberger I, Saboor S, Hilbe J, Ertl M, Ammenwerth E, et al. Measurement and quantification of generalized tonic–clonic seizures in epilepsy patients by means of accelerometry—an explorative study. Epilepsy Res 2011;95(1–2):173–83.
[36] van Andel J, Ungureanu C, Petkov G, Kalitzin S, Gutter T, de Weerd A, et al. Multimodal, automated detection of nocturnal motor seizures at home: is a reliable seizure detector feasible? Unpublished results.
[37] Van de Vel A, Cuppens K, Bonroy B, Milosevic M, Van Huffel S, Vanrumste B, et al. Long-term home monitoring of hypermotor seizures by patient-worn accelerometers. Epilepsy Behav 2013;26(1):118–25.
[38] Beniczky S, Polster T, Kjaer TW, Hjalgrim H. Detection of generalized tonic–clonic seizures by a wireless wrist accelerometer: a prospective, multicenter study. Epilepsia 2013;54(4):e58–61.
[39] Carlson C, Arnedo V, Cahill M, Devinsky O. Detecting nocturnal convulsions: efficacy of the MP5 monitor. Seizure 2009;18(3):225–7.
[40] Conradsen I, Beniczky S, Wolf P, Jennum P, Sorensen HBD. Evaluation of novel algorithm embedded in a wearable sEMG device for seizure detection. Conf Proc IEEE Eng Med Biol Soc 2012;2048–51.
[41] Fulton S, Van Poppel K, McGregor A, Ellis M, Patters A, Wheless J. Prospective study of 2 bed alarms for detection of nocturnal seizures. J Child Neurol 2013;28(11):1430–3.

[42] Kramer U, Kipervasser S, Shlitner A, Kuzniecky R. A novel portable seizure detection alarm system: preliminary results. J Clin Neurophysiol 2011;28(1):36–8.
[43] Larsen SN, Conradsen I, Beniczky S, Sorensen HB. Detection of Tonic Epileptic Seizures Based on Surface Electromyography. Conf Proc IEEE Eng Med Biol Soc 2014;942–5.
[44] Lockman J, Fisher RS, Olson DM. Detection of seizure-like movements using a wrist accelerometer. Epilepsy Behav 2011;20(4):638–41.
[45] Narechania AP, Garić II, Sen-Gupta I, Macken MP, Gerard EE, Schuele SU. Assessment of a quasi-piezoelectric mattress monitor as a detection system for generalized convulsions. Epilepsy Behav 2013;28(2):172–6.
[46] Patterson AL, Mudigoudar B, Fulton S, McGregor A, Van Poppel K, Wheless MC, et al. SmartWatch by SmartMonitor: assessment of seizure detection efficacy for various seizure types in children: a large prospective single-center study. Pediatr Neurol 2015;53(4):309–11.
[47] Poh MZ, Loddenkemper T, Reinsberger C, Swenson NC, Goyal S, Sabtala MC, et al. Convulsive seizure detection using a wrist-worn electrodermal activity and accelerometry biosensor. Epilepsia 2012;53(5):e93–7.
[48] Sabesan S, Sankar R. Improving long-term management of epilepsy using a wearable multimodal seizure detection system. Epilepsy Behav 2015;46:56–7.
[49] Szabó CÁ, Morgan LC, Karkar KM, Leary LD, Lie OV, Girouard M, et al. Electromyography-based seizure detector: preliminary results comparing a generalized tonic-clonic seizure detection algorithm to video-EEG recordings. Epilepsia 2015;56(9):1432–7.
[50] Van Poppel K, Fulton SP, McGregor A, Ellis M, Patters A, Wheless J. Prospective study of the Emfit movement monitor. J Child Neurol 2013;28(11):1434–6.
[51] Teohari V-M, Ungureanu C, Bui V, Arends J, Aarts RM. Epilepsy seizure detection app for wearable technologies. Conference Proceedings Aml. .
[52] van Andel J, Ungureanu C, Aarts R, Leijten F, Arends J. Using photoplethysmography in heart rate monitoring of patients with epilepsy. Epilepsy Behav 2015;45:142–5.
[53] Renevey P, Vetter R, Krauss J, Celka P, Depeursinge Y. Wrist-located pulse detection using IR signals, activity and nonlinear artifact cancellation. Conf Proc IEEE Eng Med Biol Soc 2001;3:3030–3.
[54] Surges R, Scott CA, Walker MC, Enhanced QT. shortening and persistent tachycardia after generalized seizures. Neurology 2010;74(5):421–6.
[55] Jansen K, Varon C, Van Huffel S, Lagae L. Peri-ictal ECG changes in childhood epilepsy: implications for detection systems. Epilepsy Behav 2013;29(1):72–6.
[56] Zijlmans M, Flanagan D, Gotman J. Heart rate changes and ECG abnormalities during epileptic seizures, prevalence and definition of an objective clinical sign. Epilepsia 2002;43(8):847–54.
[57] Jeppesen J, Beniczky S, Johansen P, Sidenius P, Fuglsang-Frederiksen A. Detection of epileptic seizures with a modified heart rate variability algorithm based on Lorenz plot. Seizure 2015;24:1–7.
[58] Ponnusamy A, Marques JL, Reuber M. Comparison of heart rate variability parameters during complex partial seizures and psychogenic nonepileptic seizures. Epilepsia 2012;53(8):1314–21.
[59] Boon P, Vonck K, van Rijckevorsel K, El Tahry R, Elger CE, Mullatti N, et al. A prospective, multicenter study of cardiac-based seizure detection to activate vagus nerve stimulation. Seizure 2015;32:52–61.
[60] Fisher RS, Afra P, Macken M, Minecan DN, Bagić A, Benbadis SR, et al. Automatic vagus nerve stimulation triggered by ictal tachycardia: clinical outcomes and device performance—the U.S. E-37 trial. Neuromodulation 2016;19(2):188–95.
[61] Khandoker AH, Karmakar CK, Palaniswami M. Comparison of pulse rate variability with heart rate variability during obstructive sleep apnea. Med Eng Phys 2011;33(2):204–9.
[62] Simon RP. Heart and lung in the postictal state. Epilepsy Behav 2010;19(2):167–71.
[63] Hirsch LJ, Donner EJ, So EL, Jacobs M, Nashef L, Noebels JL, et al. Abbreviated report of the NIH/NINDS workshop on sudden unexpected death in epilepsy. Neurology 2011;76(22):1932–8.
[64] Poets CF. Apparent life-threatening events and sudden infant death on a monitor. Paediatr Respir Rev 2004;5(Suppl. A):S383–6.
[65] Binks AP, Banzett RB, Duvivier C. An inexpensive, MRI compatible device to measure tidal volume from chest-wall circumference. Physiol Meas 2007;28(2):149–59.
[66] O'Regan ME, Brown JK. Abnormalities in cardiac and respiratory function observed during seizures in childhood. Dev Med Child Neurol 2005;47(1):4–9.
[67] Richerson GB, Buchanan GF. The serotonin axis: shared mechanisms in seizures, depression, and SUDEP. Epilepsia 2011;52(Suppl. 1):28–38.
[68] Ritchie JE, Williams AB, Gerard C, Hockey H. Evaluation of a humidified nasal high-flow oxygen system, using oxygraphy, capnography and measurement of upper airway pressures. Anaesth Intensive Care 2011;39(6):1103–10.
[69] Corbishley P, Rodríguez-Villegas E. Breathing detection: towards a miniaturized, wearable, battery-operated monitoring system. IEEE Trans Biomed Eng 2008;55(1):196–204.
[70] Jansen K, Varon C, Van Huffel S, Lagae L. Ictal and interictal respiratory changes in temporal lobe and absence epilepsy in childhood. Epilepsy Res 2013;106(3):410–6.
[71] Loddenkemper T, Kellinghaus C, Gandjour J, Nair DR, Najm IM, Bingaman W, et al. Localising and lateralising value of ictal piloerection. J Neurol Neurosurg Psychiatry 2004;75(6):879–83.
[72] Rémi J, Silva Cunha JP, Vollmar C, Topcuoglu ÖB, Meier A, Ulowetz S, et al. Quantitative movement analysis differentiates focal seizures characterized by automatisms. Epilepsy Behav 2011;20(4):642–7.
[73] Poh MZ, McDuff DJ, Picard RW. Advancements in noncontact, multiparameter physiological measurements using a webcam. IEEE Trans Biomed Eng 2011;58(1):7–11.
[74] Van Looy W, Cuppens K, Bonroy B, Van de Vel A, Ceulemans B, Lagae L, et al. Detection of body movement using optical flow and clustering. Conf Proc PoCA 2011;29–35.
[75] Lu H, Pan Y, Mandal B, Eng HL, Guan C, Chan DW. Quantifying limb movements in epileptic seizures through color-based video analysis. IEEE Trans Biomed Eng 2013;60(2):461–9.
[76] Garbey M, Sun N, Merla A, Pavlidis I. Contact-free measurement of cardiac pulse based on the analysis of thermal imagery. IEEE Trans Biomed Eng 2007;54(8):1418–26.
[77] Murthy JN, van Jaarsveld J, Fei J, Pavlidis I, Harrykissoon RI, Lucke JF, et al. Thermal infrared imaging: a novel method to monitor airflow during polysomnography. Sleep 2009;32(11):1521–7.
[78] Cuppens K, Chen CW, Wong KB, Van de Vel A, Lagae L, Ceulemans B, et al. Using spatio-temporal interest points (STIP) for myoclonic jerk detection in nocturnal video. Conf Proc IEEE Eng Med Biol Soc 2012;4454–7.
[79] Li C, Lin J, Xiao Y. Robust overnight monitoring of human vital signs by a noncontact respiration and heartbeat detector. Conf Proc IEEE Eng Med Biol Soc 2006;1:2235–8.
[80] Suzuki S, Matsui T, Kawahara H, Ichiki H, Shimizu J, Kondo Y, et al. A noncontact vital sign monitoring system for ambulances using dual-frequency microwave radars. Med Biol Eng Comput 2009;47(1):101–5.
[81] Shankar R, Jory C, Tripp M, Cox D, Hagenow K. Monitoring nocturnal seizure in vulnerable patients. Learn Disabil Pract 2013;16(9):36–8.
[82] Blum AS. Respiratory physiology of seizures. J Clin Neurophysiol 2009;26(5):309–15.
[83] Chung SS, Gerber P, Kirlin KA. Ictal eye closure is a reliable indicator for psychogenic nonepileptic seizures. Neurology 2006;66(11):1730–1.
[84] Bonnet S, Héliot R. A magnetometer-based approach for studying human movements. IEEE Trans Biomed Eng 2007;54(7):1353–5.
[85] Luca S, Karsmakers P, Cuppens K, Croonenborghs T, Van de Vel A, Ceulemans B, et al. Detecting rare events using extreme value statistics applied to epileptic convulsions in children. Artif Intell Med 2014;60:89–96.
[86] De Cooman T, Van de Vel A, Ceulemans B, Lagae L, Vanrumste B, Van Huffel S. Online detection of tonic-clonic seizures in pediatric patients using ECG and low-complexity incremental novelty detection. Conf Proc IEEE Eng Med Biol Soc 2015;5597–600.
[87] van Andel J, Thijs RD, de Weerd A, Arends J, Leijten F. Non-EEG based ambulatory seizure detection designed for home use: what is available and how will it influence epilepsy care. Epilepsy Behav 2016;57(Pt. A):82–9.
[88] Jory C, Shankar R, Coker D, McLean B, Hanna J, Newman C. Safe and sound: a systematic literature review of seizure detection methods for personal use. Seizure 2016;36:4–15.